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Patent Foramen Ovale Closure Using a Bioabsorbable Closure Device

Safety and Efficacy at 6-Month Follow-Up

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Objectives The aim of this study was to assess the mid-term safety and efficacy of percutaneous patent foramen ovale (PFO) closure using a bioabsorbable device (BioSTAR, NMT Medical, Boston, Massachusetts).

Background Closure of PFO in patients with cryptogenic stroke has proven to be safe and effective using different types of permanent devices.

Methods All consecutive patients who underwent percutaneous PFO closure with the bioabsorbable closure device between November 2007 and January 2009 were included. Residual shunt was assessed using contrast transthoracic echocardiography.

Results Sixty-two patients (55% women, mean age 47.7 ± 11.8 years) underwent PFO closure. The in-hospital complications were a surgical device retrieval in 2 patients (3.2%), device reposition in 1 (1.6%), and a minimal groin hematoma in 6 patients (9.7%). The short-term complications at 1-month follow-up (n = 60) were a transient ischemic attack in the presence of a residual shunt in 1 patient and new supraventricular tachycardia in 7 patients (11.3%). At 6-month follow-up (n = 60), 1 patient without residual shunt developed a transient ischemic attack and 1 developed atrial fibrillation. A mild or moderate residual shunt was noted in 51.7%, 33.9%, and 23.7% after 1-day, 1-month, and 6-month follow-up, respectively. A large shunt was present in 8.3%, 3.4%, and 0% after 1-day, 1-month, and 6-month follow-up.

Conclusions Closure of PFO using the bioabsorbable device is associated with a low complication rate and a low recurrence rate of embolic events. However, a relatively high percentage of mild or moderate residual shunting is still present at 6-month follow-up. (J Am Coll Cardiol Intv 2010;3: 968–73) © 2010 by the American College of Cardiology Foundation

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Percutaneous patent foramen ovale (PFO) closure has been advocated as an alternative strategy to anticoagulation or antiplatelet therapy to prevent recurrence of cryptogenic stroke in young patients. Although a number of series have suggested that percutaneous closure may be superior, no data from randomized trials are available and long-term data on the effectiveness of transcatheter closure are limited (1–3). Currently, the available closure devices consist of a metal framework and a permanent, synthetic fabric in which defect closure is achieved through a combination of mechanical closure and fibrous encapsulation. Despite the efficacy of these devices, potential complications such as friction lesions, perforations, inflammation, arrhythmias, and thrombus formation have been described, even at long-term follow-up (4–6). Furthermore, these implants will obstruct a potential transseptal access to the left atrium for future treatment of acquired heart disease.

Therefore, new strategies of PFO closure without a permanently implanted device have been explored (7–9). One of these new developments is the BioSTAR device (NMT Medical, Boston, Massachusetts), which consists of a metal framework and a totally bioabsorbable matrix. We report the mid-term safety and efficacy of percutaneous PFO closure with this novel device.

Methods

Patient group. From November 2007 to January 2009, 62 consecutive patients (55% women, mean age 47.7 ± 11.8 years) underwent PFO closure with the BioSTAR device (NMT Medical). Most patients were referred by neurologists, mainly because of cryptogenic stroke or transient ischemic attack (TIA) (93.5%). One patient (1.6%) had suffered a renal infarction, and 3 patients (4.8%) had decompression illness. The study protocol was approved by the local ethics committee. Patients' characteristics and indications for closure are listed in Table 1.

Pre-procedure evaluation. All patients underwent comprehensive neurologic evaluation. An embolic event was considered to be due to paradoxical embolism when a PFO was present and any other obvious cardiac, aortic, or cerebrovascular cause was excluded. All patients were assessed by a standardized protocol before closure, including contrast transthoracic echocardiography (cTTE) with second harmonic imaging and/or contrast transesophageal echocardiography. Agitated saline contrast was injected into an antecubital vein to demonstrate right-to-left shunt, both at rest and following the Valsalva maneuver. Microbubbles were counted in the left atrium within 3 cardiac cycles after right heart opacification. As described by Attaran et al. (10), an acceptable Valsalva maneuver is one in which the interatrial septum is seen to shift to the left, most dramatically upon the release phase. The study protocol was based on a training phase including up to 3 Valsalva maneuver attempts. The patient was asked to press against the closed glottis for at least 10 s, until septal shifting was observed. Then, contrast was injected as a rapid bolus that should have resulted in complete opacification of the right atrium. At that time point, the patient was asked to release pressure. If the contrast injection or the visualization was suboptimal, the test was repeated. An atrial septal aneurysm (ASA) was defined as a maximal protrusion of the interatrial septum, or a part of it, ≥15 mm beyond the plane of the septum. The PFO characteristics are shown in Table 1.

Device description. The BioSTAR device (Fig. 1) is the first septal occluder with a totally biodegradable matrix, which is mounted on the MP35N STARFlex "double-umbrella" framework (NMT Medical). The left and right atrial umbrellas are connected by microsprings, serving a self-centering mechanism. The matrix consists of an acellular porcine intestinal collagen layer, coated with a heparin-benzalkonium-chloride complex, which showed reduced thrombus formation in animal models (7). Furthermore, accelerated neo-endothelialization and a lower immune response was seen compared with the STARFlex device in a sheep model (11). The matrix was rapidly incorporated into the interatrial septum, leading to a low profile and early sealing of the defect. Remodeling of the matrix already started after 30 days and over a period of 2 years, it is completely replaced by host tissue.

Abbreviations and Acronyms

ASA = atrial septal aneurysm
cTTE = contrast transthoracic echocardiography
PFO = patent foramen ovale
SVT = supraventricular tachycardia
TEE = transesophageal echocardiography
TIA = transient ischemic attack

The BioSTAR device is available in sizes 23, 28, and 33 mm.

Percutaneous PFO closure. As describe previously, all procedures were performed in the cardiac catheterization laboratory, under general anesthesia and transesophageal echocardiography (TEE) guiding in the first 6 patients, and under local anesthesia with intracardiac echocardiographic guiding thereafter (12). Concomitant fluoroscopic guidance was used in all patients. The right femoral vein was used to advance a multipurpose catheter, to cross the PFO. The left femoral vein was used in case of intracardiac echocardiographic guiding. Intravenous heparin (5,000 IE) and prophylactic antibiotics were administered. Delivery and deployment of the BioSTAR device are similar to that previously described for the STARFlex device (13,14). All patients were pre-treated with aspirin and clopidogrel.

Successful device implantation was defined as completion of the procedure without the occurrence of major events (death, device embolization, device malpositioning with replacement, or need for surgical intervention). Complications were divided into major and minor complications according to the classification scheme of Khairy et al. (15).

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Table 1. Baseline Characteristics (n = 62)

Mean age ± SD, yrs	47.7 ± 11.8
Women	34 (54.8)
Weight, kg	78.3 ± 13.4
BP systolic, mm Hg	130.7 ± 14.8
BP diastolic, mm Hg	78.9 ± 8.4
Risk factors	
Smoking	13 (21.0)
Diabetes	3 (4.8)
Arterial hypertension	18 (29.0)
Hypercholesterolemia	21 (33.9)
Family history	20 (32.3)
Coronary artery disease	5 (8.1)
PFO characteristics	
RLS Valsalva	62 (100)
RLS spontaneously	24 (38.7)
Aneurysm IAS	25 (40.3)
Indication for closure*	
TIA, single	20 (32.3)
TIA, multiple	14 (22.6)
CVA, single	26 (41.9)
CVA, multiple	4 (6.5)
Decompression illness	3 (4.8)
Renal infarction	1 (1.6)
SVT	7 (11.3)

Values are mean ± SD or n (%). *Six patients had a history of both a TIA and a CVA.
BP = blood pressure; CVA = cerebrovascular accident, IAS = interatrial septum; PFO = patent foramen ovale; RLS = right-to-left shunt; SVT = supraventricular tachycardia; TIA = transient ischemic attack.

Follow-up evaluation. Within 24 h after closure, an electrocardiogram, chest X-ray, and cTTE were performed. All patients were discharged on aspirin 100 mg once a day for a period of 6 months and clopidogrel 75 mg once a day for 1 month. Antiplatelet therapy was continued in cases of persistence of residual shunting on follow-up cTTE or if there was another indication. In patients on oral anticoagulant therapy before the procedure, clopidogrel was added for 1 month. Infective endocarditis prophylaxis was recommended for 6 months.

All patients were scheduled for cTTE (with Valsalva maneuver) at 1 month, 6 months, 1 year, and 2 years to determine residual shunting, which was categorized as follows: small shunt (<30 bubbles in the left atrium), moderate shunt (30 to 100 bubbles in the left atrium), and severe shunt (>100 bubbles in the left atrium). All echocardiographic examinations were reviewed by 2 independent physicians. The 6-month TTE was combined with a visit to the outpatient clinic where a limited history and physical examination were obtained. New-onset supraventricular tachycardias (SVT) were diagnosed by a 12-lead electrocardiogram or 24-h Holter monitoring. Patients with suspected recurrent stroke or TIA were re-examined by a neurologist, and a new imaging study of the brain (computed tomography or magnetic resonance imaging) was performed. Only definite recurrent cerebrovascular events were included in the analysis.

Statistical analysis. Descriptive statistics were used to describe patients' characteristics. Continuous variables with normal distribution are presented as mean ± SD. Univariate statistical analysis was used to identify risk factors for residual shunting and the development of new SVT after PFO closure. Predictors of untoward events were analyzed by means of the Student *t* test and Fisher exact test for continuous and categorical variables, respectively. For within-group comparison of proportions, the McNemar test was used. No formal adjustment for multiple comparisons was used. $p < 0.05$ was considered to be statistically significant. All statistical analyses were performed by using SPSS software version 14.0 for Windows (SPSS Inc., Chicago, Illinois).

Results

Procedural and in-hospital outcome. Device implantation was successful in 59 patients (95.2%). In 1 patient, a 28-mm device was pushed through the PFO in the left atrium, recovered into the delivery system, and successfully replaced by a 33-mm device during the same session. In another patient, the deployed device could not be retracted into the delivery system and therefore a femoral vein incision was needed to retrieve it. In a 75-year-old man with hypertension and recurrent TIAs, in which other thromboembolic sources were firmly excluded, the closure device embolized to the aorta, was retracted percutaneously by means of a snare into the femoral artery, and removed by the surgeon. There was no ASA or any other structural heart disease on his baseline TTE. Both patients received an Amplatzer

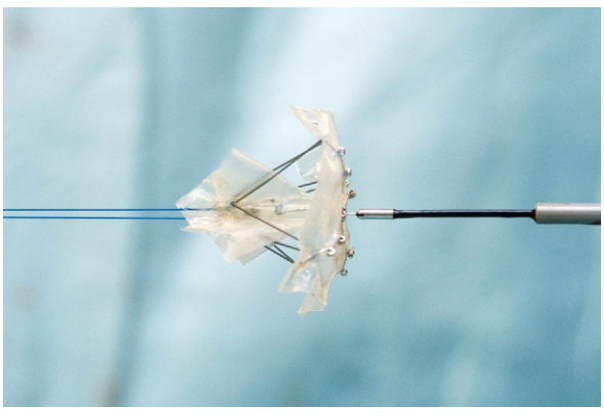

Figure 1. The BioSTAR Device

The biodegradable matrix is mounted on the MP35N STARFlex "double-umbrella" framework. The left and right atrial umbrellas are connected by microsprings, serving as a self-centering mechanism.

Table 2. Procedural Characteristics

Diameter device	
23 mm	1 (1.6)
28 mm	53 (85.5)
33 mm	8 (12.9)
Anesthesia	6 (9.6)
Echocardiographic guidance	
TEE	6 (9.6)
ICE	56 (90.4)
Radiation dose, gy/cm^2	31.1 ± 26.9
Procedural complications	
Device reposition	1 (1.6)
Minimal surgical intervention	2 (3.2)
Hospitalization stay, days	2

Values are n (%) or mean ± SD.
ICE = intracardiac echocardiography; TEE = transesophageal echocardiography.

Septal Occluder device (AGA Medical Corp., Plymouth, Minnesota) 1 month later. Furthermore, 6 patients (9.7%) had a minimal groin hematoma before discharge. There were no procedural deaths and none of the procedural complications resulted in mid-term sequelae. Procedural characteristics are listed in Table 2 and in-hospital complications in Table 3.

Mid-term outcome. COMPLICATIONS. During 6-month follow-up (n = 60), no major complications occurred (Table 3). Eight patients (12.9%) developed a new SVT, 7 of which during the first month. In 2 patients, Holter monitoring showed nonsustained atrial tachycardia for which no further treatment seemed indicated. Five patients were successfully treated for a short period with antiarrhythmic drugs and 1 patient with therapy-resistant atrial fibrillation required electrical conversion. No predictor for the development of SVT after PFO closure could be identified using univariate analysis.

RECURRENT THROMBOEMBOLIC EVENTS. There were 2 recurrent TIAs. One TIA occurred within 3 weeks after PFO closure in a patient who was still on dual antiplatelet therapy. There was an atrial septum aneurysm present on baseline echo and cTTE at discharge revealed a moderate residual shunt. An additional TTE a few days after the event did not reveal any thrombus on the device; however, there was still a small residual shunt present. Dual antiplatelet therapy was continued and at 6-month follow-up, cTTE did not reveal any residual shunt. A second TIA was noticed in another patient in the absence of a residual shunt or thrombus formation. Therefore, the TIA should not be related to a cardioembolic source. Both patients clinically recovered fully within 12 h after onset of symptoms.

RESIDUAL SHUNT. The percentage of patients with complete occlusion after PFO closure with the BioSTAR device progressively increased during follow-up. Complete PFO closure was achieved in 40%, 62.7%, and 76.3% after 1 day, 1 month, and 6 months of follow-up, respectively. Mild or moderate residual shunt was present in 51.7%, 33.9%, and 23.7% after 1 day, 1 month, and 6 months of follow-up and a large shunt was present in 8.3%, 3.4%, and 0% after 1 day, 1 month, and 6 months of follow-up, respectively (Fig. 2). Unfortunately, no predictor for the presence of a residual shunt at 6-month follow-up could be identified using univariate analysis.

Table 3. Complications and Reoccurrence of Stroke

Characteristics	In Hospital	1 Month	6 Months
n	62	60	60
Major complications			
Minimal surgical intervention	2 (3.2)	0	0
Minor complications			
New SVT	0	7 (11.3)	1 (1.6)
Inguinal hematoma	6 (9.7)	0	0
Reposition device	1 (1.6)	0	0
Reoccurrence ischemic event			
TIA	0	1 (1.6)*	1 (1.6)†
CVA	0	0	0

Values are n or n (%). *With residual shunt; †without residual shunt.
Abbreviations as in Table 1.

Discussion

As far as we know, this is the largest series of consecutive patients treated with the BioSTAR device. Our data demonstrate that percutaneous closure with the bioabsorbable device can be performed with a high success rate, a low complication rate, and that it is associated with a low risk for stroke recurrence during mid-term follow-up. Residual shunts decline gradually and no large shunts could be detected 6 months after closure.

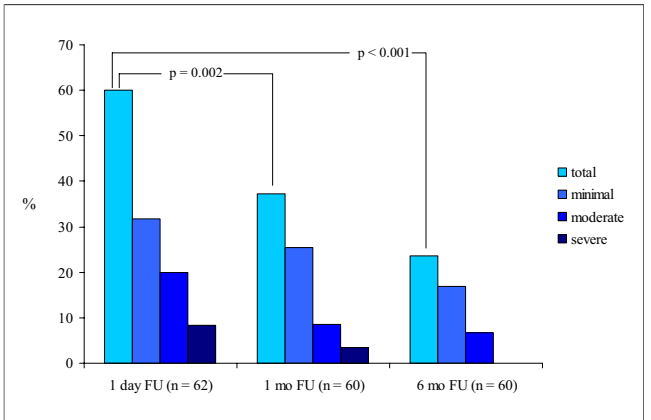

Figure 2. Residual Shunt Rate by Contrast TTE

This figure shows the residual shunt rate during follow-up assessed by contrast transthoracic echocardiography (TTE). The shunt declines gradually during follow-up (FU), but there is still 23.7% residual shunting (mild or moderate) 6 months after defect closure.

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The major advantage of using a biodegradable device should be that only a minimal amount of foreign material (i.e., the framework) remains on the interatrial septum, thus minimizing the potential risk for future complications. Furthermore, the "natural healing" of the defect and replacement of the device by host tissue should result in an earlier defect closure and a lower immune response. Those advantages were outlined in animal studies and the first in human trial showed excellent results regarding safety and efficacy (7,11,16).

Complications. In the BEST (BioSTAR Evaluation Study) (16), 58 patients (54 PFO, 4 atrial septal defect) with a mean age of 46 ± 8 years were treated with the BioSTAR device. Successful device implantation was achieved in 98% of the patients; 1 device prolapsed into the right atrium in an attempt to close an atrial septal defect and was replaced by an alternative device. In a patient with a PFO and a thick septum secundum, a 28-mm device was malpositioned and successfully replaced by a 33-mm device. No other procedural complications were noticed. Our procedural success rate was 95.2%; 1 device was malpositioned and replaced by a larger one. In this patient, a long tunnel PFO was present that was underestimated on echocardiography. Furthermore, we had 1 arterial device embolization and 1 device that had to be removed from the femoral vein after dislodgement from the septum and partial retrieval into the sheath. A possible explanation for these complications is that the BioSTAR device is very soft and flexible. Furthermore, both cases occurred in our learning phase using intracardiac echocardiography and therefore could be related to less adequate visualization. Six of our patients (9.7%) developed a minimal groin hematoma, but none required blood transfusion.

Atrial rhythm disturbances are a common short-term complication using transseptal devices. Despite the low profile and the presumed rapid endothelialization of the BioSTAR device, the incidence of new SVT in our study was 12.9%, which is comparable to the frequency of 7% to 15% reported in series with other devices (17,18). We did not observe any relationship between the occurrence of SVT and device size or the presence of an ASA.

Reoccurrence of thromboembolic events. The recurrence rate of stroke or TIA in our observation is low (3.2%) and concordant with findings previously reported. Two systematic reviews (1,15) suggest that percutaneous PFO closure is more effective than medical treatment regarding secondary prevention of embolic events (recurrence rate: 0% to 4.9% vs. 3.8% to 12% at 1 year). We did not detect any thrombus on the device in those 2 patients, but we realize that thrombus assessment with TTE only might be suboptimal.

Residual shunt. The residual shunt rate 6 months after PFO closure ranges from 8% to 20% (19,20). At 6 months, a mild or moderate residual shunt was observed in 23.7% of our study population. Direct comparison of the results of these studies is difficult because different types of devices and different methodological descriptions were used. Our method of shunt grading showed an excellent interobserver variability using cTTE (21). In contrast to other investigators, who described predictors of residual shunt, such as the presence of ASA, larger PFO size, and larger device size (22–24), we could not identify predictive factors regarding residual shunt. Therefore, we must hypothesize that the BioSTAR device itself does not "close the door" appropriately. However, rapid endothelialization and defect closure was seen in a sheep model, the natural healing of the defect induced by the matrix of the device may be postponed in some patients. Maybe, the role of platelets and platelet-inhibition is underestimated. When platelets are activated as a result of endothelial damage during PFO closure, they stimulate smooth muscle cell proliferation and migration and contribute to the synthesis of connective tissue. Hence, when we treat our patients with aspirin and clopidogrel after PFO closure, the formation of neo-endothelium and the natural healing induced by the BioSTAR device could be diminished. It is also known that there is a substantial interpatient variability regarding inhibition of platelet aggregation/activation with aspirin and clopidogrel. To underline our hypothesis, we must state that the sheep in the animal model, which did show early endothelialization, were not treated with antiplatelet agents.

The 2 other studies (16,25) regarding PFO closure using the BioSTAR device, report a much lower residual shunt rate. However, in BEST (16), only moderate and large shunts were reported. As a result, 4% residual shunting was seen at 6 months using cTTE. In another report (25), no residual shunt was observed in 19 patients, 6 months after PFO closure; however, the TTE studies were performed without contrast. On the other hand, 4 of these patients (21%) had a trivial shunt on contrast-transcranial Doppler.

Maybe, our meticulous Valsalva maneuver protocol resulted in a higher amount of residual shunt when compared to the 2 previous studies.

Despite the high prevalence of residual shunting in our group, only 1 patient suffered a reoccurrence of TIA. It is known that the persistence of a significant shunt has been identified as a risk factor for embolic recurrence. On the other hand, it has been outlined that especially small shunts may close late; therefore, we will repeat cTTE at 1 year and 2 years after defect closure.

Study limitations. First, our patient population was a selected cohort referred for percutaneous PFO closure, and there may be substantial differences with other series regarding patient selection and implantation technique. Second, it is a single-center study with a relative small number of patients and a short follow-up time. Third, during follow-up, we performed contrast TTE instead of contrast TEE, which is still defined as the "gold standard" for the detection of interatrial shunts. However, TEE is semi-invasive, time-

consuming, and the performance of an adequate Valsalva maneuver is invariably impaired. Furthermore, contrast TTE with second harmonic imaging, as used in our study, seems to be a very good alternative for TEE as a first-line exam (26).

Conclusions

Percutaneous closure of symptomatic PFO using the BioSTAR device seems to be safe and efficient, according to the low complication rates and the low recurrence rate of TIA/stroke. However, a relative high percentage of residual shunting is present 6 months after closure. The BioSTAR device was developed to extinguish potential complications that are inherent to permanent closure devices. We did not observe a decrease in atrial rhythm disturbances during the first month after closure. Nevertheless, we will perform long-term follow-up and hopefully ascertain the true advantages of this new device when it is gradually absorbed over time.

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Key Words: closure ■ device ■ patent foramen ovale ■ transseptal catheter.